COMPOSITIN AND METHOD FOR POST-SURGICAL ADHESION REDUCTION WITH THERMO-IRREVERSIBLE GELS OF POLYOXYALKYLENE POLYMERS AND IONIC POLYSACCHARIDES

This is a continuation-in-part of copending application Ser. No. 517,283 filed on May 1, 1990 which is a continuation-in-part of Ser. No. 07/449,215 filed Dec. 12, 1989, which is a divisional application of Ser. No. 07,272,199 now U.S. Pat. No. 4,911,926.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to methods and compositions for reducing post-surgical adhesions in the mammalian abdominal or thoracic cavity or other body spaces, whether accidentally or surgically created.

2. Description of the Prior Art

There is a need for a method and composition suitable for use in preventing adhesion formation/reformation in mammals following injury to the organs of the peritoneal, pelvic or plural cavity, or other body spaces, such as subdural, extraocular, intraocular, otic, synovial, tendon sheath, whether accidentally or surgically created.

According to Ellis in a review entitled "The Cause And Prevention Of Post-operative Intraperitoneal Adhesions" in *Surgery, Gynecology and Obstetrics* for Sep. 1971, volume 133, pages 497–509, at pages 502–503, the prevention of adhesions has been the subject of an enormous amount of work since the beginning of this century. According to Ellis, these attempts have included means of preventing the fibrin-coated walls of the intestine from reaching each other by distending the abdomen with oxygen or filling the abdomen with saline solution, paraffin, olive oil, lanolin, concentrated dextrose solution, macromolecular solutions of all sorts, and silicones.

Menzies and Ellis in a article entitled "Intestinal Obstruction from Adhesions—How Big is the Problem?". *Annals of the Royal College of Surgeons* of England, volume 72, pages 60–63, 1990 reported adhesions findings in 10.4% of 115 patients with first-time laparotomies while 93% of 210 patients had intra-abdominal adhesions due to previous surgery. Admission for intestinal obstruction was made for 0.9% of 28,297 general surgery patients while 3.3% of 4,502 laparotomy patients were admitted for adhesive obstruction. These data emphasize the magnitude of readhesion after adhesiolysis or from subsequent surgical procedures. The authors state on p. 62, that there is currently no effective treatment that prevents the recurrence of lysed adhesions.

Caspi, Halperin, and Bukovsky in an article entitled "The Importance of Periadnexal Adhesions in Reconstructive Surgery for Infertility" appearing in *Fertility and Sterility* for Mar. 1982, volume 31, number 3, pages 296–300, at page 299 indicate that despite experimental and clinical efforts in the prevention of adhesion formation following surgery, no major advances have thus far been achieved. The authors discuss the use of post-operative intraperitoneal installation of a mixture of hydrocortisone acetate (a glucocorticoid), promethazine, and ampicillin. As an alternative method of treatment, a low molecular weight dextran (a branched polysaccharide composed of glucose units) was also instilled intraperitoneally in another group of patients. The authors conclude that the intraperitoneal installation of high doses of glucocorticoids combined with early hydrotubations seems to be a worthwhile method.

Musich and Behrman in an article entitled "Infertility Laparoscopy In Perspective: Review of 500 Cases" appearing in *The American Journal of Obstetrics and Gynecology* for Jun. 1, 1982, pages 293–303, at page 300 in the discussion section of the article disclose that there is a need to prevent adhesions subsequent to surgery in view of a study of 35 patients which indicated that 30 of these patients having previous tuboplasties had severe adhesions, one-third of which were judged to be inoperable.

High molecular weight dextran either alone or in combination with dextrose has been used in the prevention of peritoneal adhesions subsequent to surgery. Dextran is clinically standardized to a low molecular weight of about 75,000 by partial hydrolysis and fractional precipitation of the high molecular weight particles which normally have molecular weights of up to 200,000. Dextran is a polymer of glucose which has a chain-like structure and is produced from sucrose by Leuconostoc bacteria. In articles appearing in *Fertility and Sterility,* volume 33, number 6, Jun. 1980, pages 660–662, Holtz, Baker, and Tsai and volume 34, number 4, Oct. 1980, pages 394–395, by Holtz and Baker, results are reported of the adhesion reducing effects of a 32% (aqueous) solution of dextran 70 containing 10% dextrose (sold under the trade name HYSKON by Pharmacia, of Piscataway, N.J.). Holtz et al postulate several mechanisms of action in the prevention of peritoneal adhesions utilizing HYSKON including a simple mechanical separation of adjacent surfaces, termed a hydroflotation effect.

Project coordinator diZerega and several contributors have reported the results of a large study in an article entitled "Reduction of Post-operative Pelvic Adhesions with Intraperitoneal 32% Dextran 70: A Prospective, Randomized Clinical Trial" in *Fertility and Sterility,* volume 40, number 5, for November 1983, pages 612–619. The authors, at page 618, indicate that the use of Dextran intraperitoneally has limitations such as the reported tendency of HYSKON to support bacterial proliferation and concern over the anaphylactoid potential of dextran. In addition, the benefit of Dextran 70 in preventing post-operative adhesions was shown to be limited to the more dependent regions of the pelvis. In U.S. Pat. No. 4,889,722 Sheffield and di Zerega disclose the use of tissue plasminogen activator in the inhibition of post-surgical adhesions.

Borten, Seibert, and Taymor in *Obstetrics and Gynecology,* volume 61, number 6, June 1983, pages 755–757 report in an article entitled "Recurrent Anaphylactic Reaction to Intraperitoneal Dextran 75 Used for Prevention of Postsurgical Adhesions". These authors indicate that anaphylactic reaction to Dextran administered intravenously is well documented and report such a reaction after intraperitoneal administration of Dextran.

Linsky in *The Journal of Reproductive Medicine* for Jan. 1987, pages 17–20 in an article entitled "Adhesion Reduction in the Rabbit Uterine Horn Model Using an Absorbable Barrier, TC-7". These authors report that the use of a resorbable fabric barrier provides a significant reduction in post-operative adhesion formation and that no gross remnants of the fabric barrier material were noted, subsequent to initial placement, after a two week period.